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Subject: NEWS UPDATES: Expert Reviewers Question EPA's Proposed Methanol Risks As Overly Strict (Risk Policy Report)

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Expert Reviewers Question EPA's Proposed Methanol Risks As Overly Strict

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A panel of expert reviewers is faulting EPA's non-cancer risk estimates for the common chemical and fuel methanol for being overly strict, with some reviewers unfavorably comparing EPA's analysis to a 2003 assessment published by the National Toxicology Program (NTP) that found common exposures to methanol pose little developmental toxicity risk.

EPA, in an unusual move, included a "bonus question" in its charge questions to the panel, asking reviewers to comment specifically on the reference concentration (RfC) and reference dose (RfD) values -- the non-cancer risk estimates EPA calculates for each Integrated Risk Information System Assessment (IRIS). "Are these numbers more conservative than they need to be to protect public health?" the agency asks.

Most of the reviewers replied that EPA had calculated overly-stringent risk estimates for methanol. Of the seven reviewers, five described concern about the usefulness or reliability of EPA's proposed RfC or RfD.

"The process of developing these RfC and RfD values has produced a result that is counter-intuitive, implying that individuals with no unusual methanol exposure may be at risk of developmental effects," writes one of the reviewers, Stephen Roberts, a professor at the University of Florida. "That's implausible, and clearly signals the need to re-evaluate how to consider background methanol concentrations in the development of credible toxicity values. What is missing from this and other IRIS toxicological reviews is an assessment, after going through the process of RfC and RfD development, whether the resulting values make sense, i.e., are they logical in the context of exposures and effects anticipated in human populations?"
Relevant documents are available on InsideEPA.com. (*Doc ID: 2384127*)

Roberts raises a concern that has been raised by critics of the IRIS assessment process for several recent draft assessments of naturally occurring chemicals, either in the human body or the environment, including arsenic, dioxin, formaldehyde and hexavalent chromium.

Roberts also cites the 2003 assessment of the NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) methanol panel. Roberts writes the panel "considered common exposures to methanol and concluded that they pose no immediate concern for developmental toxicity . . . This appears to be a reasonable conclusion and creates a real credibility problem for the proposed methanol RfC and RfD."

Similarly, another reviewer, David Dorman, also urges EPA to consider the work of the NTP methanol panel, specifically with regard to the proposed RfC. "My greatest reservation about the EPA's proposed RfC value relates to the observation that exposures at (or slightly above) the RfC would result in a change in blood methanol concentration that falls within the range of normal values seen in people. This value becomes difficult to defend scientifically for an endogenous chemical like methanol," Dorman writes.

Dorman, a professor at the North Carolina State University veterinary school, continues, "Ultimately, the EPA team should ask the question when a change in blood methanol concentration may lead to a toxicologically significant effect. This approach was considered by the NTP CERHR group that considered a blood methanol concentration of [less than 10 milligrams of methanol per liter of blood (mg/L)] to not be associated with adverse developmental effects. This determination considered the available toxicity data from people and animals and normal blood methanol concentrations seen in people with various dietary inputs."

NTP's CERHR program, which operated between 1998 and 2010, only assessed environmental substances for their potential adverse reproductive or developmental effects -- not any other endpoints. The abstract for the CERHR methanol monograph concludes "there is concern for adverse developmental effects in fetuses if pregnant women are exposed to levels of methanol that result in high blood concentrations, such as with acute methanol poisoning . . . Second, for exposures that result in low blood methanol concentrations (below approx. 10 mg/L blood), there is minimal concern for adverse developmental effects, and negligible concern for adverse male reproductive effects. There is insufficient evidence to assess the effects of methanol on female reproduction. Data available to the expert panel were not sufficient to rule out the possibility of male reproductive effects at toxic exposure levels. The panel judged that blood levels [greater than or equal to] 10 mg/L are not expected to result from normal dietary or occupational exposures."

The concerns come as EPA seeks to finalize its non-cancer assessment for methanol -- after splitting the assessment in two separate documents following controversy over data the agency used to calculate its cancer potency estimates for the chemical (*Risk Policy Report*, April 12). EPA proposed a tightened RfD, or the amount below which it is believed to be reasonably safe to ingest daily over a lifetime without increased risk of adverse effects, to 0.4 milligrams per kilogram body weight per day (mg/kg-day) from its previous 1991 estimate of 0.5 mg/kg-day.

EPA also proposes a first-time RfC, or estimated amount of the chemical considered reasonably safe to inhale daily over a lifetime without adverse effects, of 2 milligrams per cubic meter of air (mg/m3). The proposed RfD and RfC in its draft non-cancer methanol assessment, released last April, are the same as those EPA released in an earlier version of the document, which also addressed methanol's cancer risks. That section of the assessment has been delayed following concerns raised about the quality of Italian studies EPA used as the basis for its cancer risk estimates. EPA announced last April that it would split the document to continue its non-cancer risk assessment of methanol. The agency last year delayed assessing methanol's cancer risks while the Italian Ramazzini studies are more fully reviewed by NTP.

One reviewer, consultant Janusz Byczkowski, notes that there is little different between EPA's existing RfD for methanol and the slightly more stringent proposed RfD. "The RfD developed in the present document is numerically almost the same as the previous one, already listed in IRIS data base," Byczkowski writes. "Although, the upper bound on concentration of normal physiological 'background' of methanol in humans has not been determined in this document, it seems that the exposure to methanol at the proposed RfD or RfC level may produce internal concentration not much different from the physiological background. . . . While the overall goal of developing reference toxicity values is to protect public health, perhaps, the revision of the current document would give an opportunity to U.S. EPA to derive RfC and RfD that would be not only health-protective, but also realistically close to the no-adverse-effect level in humans, with reasonable margin of safety and appropriate confidence."

Two of the reviewers also note that the EPA's standard approach to developing its IRIS assessments led to the overly conservative risk estimates. These long-held conservative default approaches that EPA uses in the instance if limited data are often the target of critical industry representatives. Dorman writes, "The proposed RfC value is the result of systematic application of multiple conservative estimates (often lacking transparency or scientific justification) and seemingly arbitrary application of additional default uncertainty factors."

Reviewer Kenneth McMartin, a professor at Louisiana State University's Health Sciences Center, also argues, "The RfD and RfC values have been appropriately derived based on the BMD/PBPK analysis utilizing 'standard EPA procedures,' but the resulting values lack scientific credence and are not logical in the sense of the exposures expected for humans." BMD, or benchmark dose, refers to the amount of the assessed substance that produces a predetermined change in response rate of an adverse effect, according to EPA's IRIS glossary. PBPK or physiologically based pharmacokinetic refers to a type of model used to estimate how a chemical travels through the body.

McMartin continues, "Because of the background level of methanol in all humans lies in the range of 2 mg/L, the projected increase in methanol level from the RfC/RfD exposure is only 0.04 mg/L, i.e. a level that is really indistinguishable from the background. The implications of this include that all humans would be susceptible to developmental effects of methanol no matter what exposure they had experienced. . . . The conundrum occurs because the PBPK model itself has built-in conservatism, the BMD calculation has built-in conservatism and then a 100-fold uncertainty is applied. All of these factors contribute to bring the 'RfC/RfD

exposure' down to the levels where there is essentially no exposure-induced increase in methanol levels above the endogenous, background level, which means there is essentially no risk." -- *Maria Hegstad*

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